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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,456	11/14/2001	Maurice Zauderer	1821.0070004/EKS/EJH/TAC	6770
26111 7590 04/02/2010 STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C. 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005				
EXAMINER				
STEELE, AMBER D				
ART UNIT		PAPER NUMBER		
1639				
MAIL DATE		DELIVERY MODE		
04/02/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

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3 RECORD OF ORAL HEARING
4 UNITED STATES PATENT AND TRADEMARK OFFICE

5
6 BEFORE THE BOARD OF PATENT APPEALS
7 AND INTERFERENCES
8
9

10 *Ex parte* MAURICE ZAUDERER and ERNEST S. SMITH
11
12

13 Appeal 2009-009521
14 Application 09/987,456
15 Technology Center 1600
16
17

18 Oral Hearing Held: March 10, 2010
19
20

21 Before TONI R. SCHEINER, DONALD E. ADAMS and
22 RICHARD M. LEOVITZ, Administrative Patent Judges.
23

24 ON BEHALF OF THE APPELLANT:
25

26 TRACY L. MULLER, ESQ.
27 ELIZABETH J. HOANES, Ph.D, ESQ.
28 Sterne Kessler Goldstein Fox P.L.L.C.
29 1100 New York Avenue, N.W.
30 Washington, D.C. 20005
31 (202) 371-2600
32
33
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1 The above-entitled matter came on for hearing on Wednesday, March
2 10, 2010, commencing at 2:14 p.m., at the U.S. Patent and Trademark Office,
3 600 Dulany Street, 9th Floor, Hearing Room A, Alexandria, Virginia, before
4 Kevin E. Carr.

5 THE USHER: Calendar Number 32: Appeal Number 2009-
6 009521, Ms. Muller.

7 JUDGE SCHEINER: Thank you. Good afternoon.

8 MS. MULLER: Good afternoon.

9 JUDGE SCHEINER: If you have a card for our reporter, that
10 would be great. If you would like to introduce your colleague for the record
11 as well. And I just want to doublecheck that this is an open hearing, because
12 we do have an observer. Whenever you're ready.

13 MS. MULLER: Okay. Thank you. May it please the Board,
14 my name is Tracy Muller, and this is my colleague from Stern Kessler
15 Goldstein and Fox, Elizabeth Hoanes. I am here today representing
16 University of Rochester and Vaccinex, Incorporated, who are the exclusive
17 licensee and the assignee of the application on appeal. And the claims on
18 appeal today are directed to a method of selecting polynucleotides that encode
19 human antibodies, and the issue on appeal is obviousness. And this is the
20 point on which we are in disagreement with the Examiner.

21 JUDGE SCHEINER: May I interrupt you for just a second?
22 There were two provisional, obviousness- type double patenting rejections,
23 but it's my understanding that the underlying applications are abandoned and
24 the rejections are moot.

25 MS. MULLER: That's absolutely correct. That is now a moot
26 issue. So we're now just addressing the regular obviousness rejection.

1 JUDGE SCHEINER: Okay.

2 MS. MULLER: And we submit that it's only through hindsight
3 that this invention has found obviousness. The invention is actually a major
4 breakthrough in the field of antibody selection technology, because it makes it
5 possible for the first time to select from two separate libraries, one of heavy
6 chains and one of light chains, in vitro, in mammalian cells, fully human
7 antibodies. And with this library you have the potential for getting say 10 to
8 the 14 possible combinations.

9 And before this invention, the way to make fully human
10 antibodies was to either use transgenic mice, which had been altered so that
11 they would express human immunoglobulin genes, or to perform an in vitro
12 type of selection through phage display, which is performed in bacterial cells.
13 And this invention now is a non-obvious technology that overcomes
14 numerous problems that are associated with those other technologies.

15 In this case, even after the Supreme Court's decision in KSR, a
16 showing of obviousness still requires an identifiable rationale or motivation to
17 combine references, and once you've come up with that, a reasonable
18 expectation of success that that modification or the combination would work.
19 And the Federal Circuit decided in "Eisai v. Dr. Reddy's Laboratory" that
20 there was a non-obvious chemical compound compared to a prior art
21 compound, and they set forth three assumptions that were necessary for the
22 KSR analysis.

23 They first said that there is a starting reference point that must be
24 assumed: one that was available to one of skill in the art; that one of skill in
25 the art might identify a problem and pursue solutions. The second point,
26 starting assumption, was that there are some reasons available also within the

1 knowledge of one of skill in the art to make the particular modifications that
2 were made that you would achieve the claimed invention. And the third
3 assumption was that there would be some reason for narrowing the universe
4 of prior art to a number of finite, identified, predictable solutions. And these
5 presumptions were also illustrated in other post-KSR cases, such as "Takada
6 v. Alpha Farm."

7 JUDGE LEBOVITZ: But the "Eisai" case had to do -- that was a
8 little different. They were talking about a lead compound. They were saying
9 you have to have a starting point.

10 MS. MULLER: Right.

11 JUDGE LEBOVITZ: And the problem, I don't remember which
12 way "Eisai" went. I think it said there was no starting compound, but once
13 you have a starting compound, a lead compound, then the question was, was
14 there reason to modify it.

15 MS. MULLER: Right. But I think also the analogy in this
16 situation is identifying the appropriate compound, that one of ordinary skill in
17 the art would have picked that compound as the lead compound.

18 JUDGE LEBOVITZ: Well, wouldn't the lead compounds in this
19 case maybe be the libraries, the two?

20 MS. MULLER: The analogy that I'm thing of is --

21 JUDGE LEBOVITZ: Right.

22 MS. MULLER: -- the selection technology is the analogy. So
23 would you start from something in a eukaryotic system, for example? Would
24 you start with Rowlands, like the Examiner did here, or would you start with
25 something like --

26 JUDGE LEBOVITZ: The phage display.

1 MS. MULLER: -- the phage display or the transgenic mice. So
2 in this case primary reference was Rowlands, which is a technology of
3 expressing a single antibody. They were interested in coming up with a way
4 to express an antibody that they could use in sufficient quantities for clinical
5 investigation. So they only wanted to take a single antibody and figure out a
6 way to make more of it.

7 JUDGE SCHEINER: So they inserted portions into vaccinia, co-
8 infected the cells.

9 MS. MULLER: Correct.

10 JUDGE SCHEINER: And --

11 MS. MULLER: And a portion, a proportion of them --

12 JUDGE SCHEINER: -- retrieved antibodies that were able to
13 assemble correctly.

14 MS. MULLER: -- a proportion of the antibodies made it into,
15 were secreted into the extracellular medium. And, actually, even if you look.

16 JUDGE LEBOVITZ: What do you mean by "a proportion?"
17 Because they were in the -- are you talking about the Rowland reference?

18 MS. MULLER: Correct.

19 JUDGE LEBOVITZ: Weren't they expressing defined light and
20 heavy chains?

21 MS. MULLER: Exactly. Only a proportion of their defined
22 heavy and light chains were actually getting expressed -- were assembling
23 together -- as heavy and light chain combinations. They actually expressed, I
24 think, two-thirds of their light chain was getting secreted, and only a fifth of
25 their heavy chain was getting secreted. So even of the amount that they were

1 making of a known antibody, only a proportion of that amount was actually
2 an assembled antibody. So in this case when you --

3 JUDGE LEBOVITZ: Where did they say that? Can you point to
4 that?

5 MS. MULLER: Sure.

6 JUDGE LEBOVITZ: Because the reason why I'm questioning
7 that or asking about that, the Examiner was relying on that as an expectation
8 of success. Because there is a system where you put in heavy chain, light
9 chain, and you get secretion. So if there's something in there that attached
10 down on that.

11 MS. MULLER: Right. If you look at page 7 of Rowlands, the
12 first paragraph that's bridging over, it says "In the system described in more
13 detail in the following examples, heavy and light chains were synthesized at
14 roughly equal levels. But it was found that only a portion of the total amount
15 of each chain which was synthesized was actually assembled."

16 JUDGE SCHEINER: But they made suggestions for how to deal
17 with that. Didn't they? How to compensate for that?

18 MS. MULLER: There were some ways to adjust with a single
19 antibody, but when you take that in look at it in the context of a library, what
20 you're doing with the library, you're not trying to express as much of one
21 thing as you can. You're trying to express a few of a lot of things across your
22 population. So I think even the suggestion of how to deal with that with one
23 antibody would not be instructive to one who's trying to do a library in a
24 eukaryotic cell.

25 JUDGE SCHEINER: Okay. Right.

1 MS. MULLER: And if you're starting from Rowlands, one of
2 ordinary skill in the art would not be looking to the single, antibody context to
3 start from that point. The Examiner in this case acknowledged that the
4 Rowlands reference doesn't teach two libraries, and then pointed to the
5 Zauderer reference, which describes how to make a single library. There are
6 basically antigens to elicit a T-cell response, and saying you could have taken
7 the instruction from that and would have known to put two libraries into the
8 Rowlands method. But, again --

9 JUDGE SCHEINER: Well, the Examiner relied on Zauderer,
10 who is our inventor. Is that correct?

11 MS. MULLER: It is the same Zauderer, yes.

12 JUDGE SCHEINER: For the disclosure of the trimolecular
13 recombination technique, which would allow you to make libraries.

14 MS. MULLER: Right. But a lot of what the Examiner was
15 doing in his arguments was pointing to the efficiency with which the libraries
16 are created, and extrapolating that to the efficiency with which he might be
17 able to screen the actual antibodies that are produced. So even though there is
18 a method for making a library in vaccinia virus, there is nothing instructive in
19 that to say, well, if you're taking separate libraries of molecules that have to
20 pair together to be expressed and functional, Zauderer doesn't provide that
21 information, which is --

22 JUDGE LEBOVITZ: But doesn't Rowlands provide that
23 information? Because if you're expressing one at a time, right, which you'd
24 be doing using this other technique to make libraries, and then you're putting
25 one at a time into the cells, wouldn't Rowlands tell you that once you do that
26 you'll get expression of at least some functional antibody?

1 MS. MULLER: Once again, the distinction is that when you're
2 putting one antibody as in Rowlands, one heavy, one light chain, this is an
3 extensively engineered antibody. It was actually a humanized antibody, so it
4 was known that in the appropriate circumstances, i.e. non-reducing conditions
5 where the disulphide bonds compare, that it binds antigen and it has optimum
6 pairing properties.

7 When you're talking about random heavy and light chain
8 molecules from libraries that you are trying to get different molecules
9 expressed in the population themselves, as opposed to as many of the same
10 antibody as you can, you're still not going to know from the fact that you
11 could make a library in Zauderer that once you put those into the Rowlands
12 method that you're going to get a sufficient proportion of those pairing, and
13 again --

14 JUDGE SCHEINER: I realize the Examiner didn't address this,
15 but what if you started with an immune library, in other words, a heavy chain
16 library constructed from an immune source, and light chain constructed from
17 the same source. I understand the Examiner didn't address this.

18 MS. MULLER: So you're saying --

19 JUDGE SCHEINER: You're not starting from --

20 MS. MULLER: -- someone who's been immunized for a
21 particular antigen.

22 JUDGE SCHEINER: Yeah.

23 MS. MULLER: I think even with an immunized subject, you
24 still get variability. I think there may be a proportion of their antibodies that
25 are directed to a particular target.

1 JUDGE SCHEINER: Okay. And I know this wasn't addressed,
2 anyway, so.

3 JUDGE LEBOVITZ: But where you were making an analogy to
4 lead compounds, wouldn't you say or what would be the lead compound in
5 this case? Are you saying that it would be the bacteria and there'd be no
6 reason to go from the bacteria to the human?

7 MS. MULLER: I think, well, you could look at it two ways. In
8 this case the Examiner is using Rowlands, I think, as the lead compound.
9 He's saying that's my lead compound. That's the primary reference. That's
10 the starting point that I would look to.

11 JUDGE LEBOVITZ: Oh.

12 JUDGE SCHEINER: But you're saying that someone of skill in
13 this art would have started with phage display library.

14 MS. MULLER: They would have either started with phage
15 display, because if you wanted to look to an in vitro system, you would look
16 to phage display.

17 JUDGE LEBOVITZ: But I didn't see you question, and maybe
18 you did. So maybe you can just go question the motivation, the reason to
19 combine, because certainly if people were doing it in bacteria. And there may
20 be reason to do it in mammalian cells because of glycosylation, but I didn't
21 see you really question the motivation to apply kind of the phage display
22 combinatorial library art to the Rowlands vaccinia virus system.

23 MS. MULLER: The reason one wouldn't have been led to that is
24 because for the reasons that we addressed in the Brief and that Dr. Storkus's
25 Declaration talked about or that you wouldn't have expected that to work in a
26 mammalian cell. That system was instructive. The prokaryotic system in

1 which you do phage display is so different that you can't just assume
2 something like that.

3 JUDGE SCHEINER: I think what we're getting at is what we're
4 trying to understand, if there's a basic disagreement with the original
5 combination, or if the argument centers on a lack of a reasonable expectation
6 of success. It seemed that that's what the Brief focused on, rather than the
7 underlying combination to begin with, and I think that what we're asking
8 about is the underlying combination.

9 MS. MULLER: I think it's a combination of both and I think
10 there's no motivation to combine them, and it's because if you looked at this
11 other system, the thinking at the time was that these were completely different
12 systems. And if you look, there's an industry survey that was submitted as
13 part of the Storkus Declaration. The Storkius Declaration was Exhibit 4 and
14 submitted as a sub exhibit to that was an industry summary, and it gave some
15 insight into what people were thinking about the different technologies at the
16 time for selecting human antibodies.

17 JUDGE SCHEINER: I'm sorry. What's our timeframe here
18 when this was filed?

19 MS. MULLER: The application was filed in 2001.

20 JUDGE SCHEINER: One, okay.

21 MS. MULLER: The survey was conducted.

22 JUDGE LBOVITZ: Where was the survey mentioned?

23 JUDGE SCHEINER: It was at the very end of this. I'm sorry.
24 Go ahead.

1 MS. MULLER: Oh, it's exhibit 4 for you should be the Storkus
2 Declaration, and it was one of the accompanying documents. It should be
3 right after his CV.

4 JUDGE LEBOVITZ: Oh, okay.

5 JUDGE SCHEINER: It's along with the paragraph that talks
6 about --

7 JUDGE LEBOVITZ: There are a number of references attached.

8 JUDGE SCHEINER: Yeah.

9 JUDGE LEBOVITZ: Yeah. Okay.

10 MS. MULLER: And in that survey there are some quotes from
11 people in the industry that the consultants were polling some industry experts
12 to see what their feelings were about current technologies. And one of the
13 comments they made was "We consider phage display. This is on slide
14 number 35, page number 35. It says, "We consider phage display to be a
15 research tool. We never seriously considered it for therapeutic purposes due
16 to the low quality of antibodies."

17 And underneath that there's another quote from a different
18 executive at Cell Tech that says, "We use mice. And if that doesn't work we
19 use rabbits." The in vivo affinity maturation in those systems produces better
20 antibodies than the phage system. So the thinking at the time was we use
21 phage, if we want in vitro screening. If we want fully human antibodies that
22 have been made in eukaryotic cells, we look at transgenic animals.

23 JUDGE SCHEINER: Okay.

24 MS. MULLER: And so using Rowlands as the starting point,
25 that isn't the place where one of ordinary skill in the art would have been
26 looking at that time. If they were looking at anything, they would have

1 looked at the phage display, but that again, because it's such a different
2 system, there was no expectation that you could just take a mammalian
3 population of host cells and do the same thing that you did with phage.

4 JUDGE LEBOVITZ: But is that just semantics in terms of, I
5 mean, there's the prior art and there are probably different ways of stating how
6 it would be obvious. But the fact is that the prior art teaches a phage display
7 system as making antibodies with using separate light and heavy chain. And
8 then the prior art teaches a mammalian cell with separate vectors, vaccinia
9 vectors. So a person of skill, sort of weighing those together, the issue is
10 would he have found what's claimed obvious. And maybe it's not so
11 important where you start with one reference or another, unlike a lead
12 compound, the Eisai reference, where it really is important that you're starting
13 at one compound.

14 MS. MULLER: But again, either way you start, the only way,
15 given what the thought at the time was to get to that point was to use the
16 claims themselves as your roadmap. Naturally, it looks obvious if you're
17 looking from the claims to go and see what else was out there that had similar
18 elements, but that's a case of cherry-picking the elements out of the art.

19 JUDGE ADAMS: Well, we have bacteria and we have a phage
20 display. Phage will infect the bacteria. Then we can produce these
21 recombination events, right, using phage display.

22 JUDGE SCHEINER: Using two separate libraries in phage
23 display.

24 JUDGE ADAMS: Right. We have eukaryotic cell. We have
25 vaccinia. Vaccinia infects the eukaryotic cell. What's so unobvious about

1 using vaccinia with a library and it has a corollary to the phage system to
2 infect the eukaryotic cell as a corollary to infecting the bacterial cell?

3 MS. MULLER: There is a difference in that if you look at the
4 Waterhouse reference. If you look at the figure, what you're putting into the
5 bacteria phage, you start with a separate library of heavy and light chains that
6 you've isolated, for example, by PCR. When you actually put them into the
7 phage, they recombine to form a single phage particle that has both a heavy
8 and a light chain in the same phage particle. So when they get expressed,
9 they get expressed together from the same particle which actually ends up
10 being one library.

11 JUDGE ADAMS: So you're suggesting that all phage display
12 systems using immuno globulins are Fv fragments?

13 MS. MULLER: No. I'm saying that within the --

14 JUDGE ADAMS: Well that's what you just said. Right?

15 MS. MULLER: No. No, let me clarify. What I'm saying is, and
16 the figure in Waterhouse on page 2266 illustrates this.

17 JUDGE LEBOVITZ: Can you give us a second to find that
18 figure?

19 MS. MULLER: Oh, sure.

20 JUDGE LEBOVITZ: What figure?

21 JUDGE SCHEINER: It's the second page.

22 MS. MULLER: It's the second. Waterhouse is only two pages.
23 That's the second page.

24 JUDGE LEBOVITZ: Okay. Thanks.

25 JUDGE SCHEINER: It's very fuzzy in ours, but we can read it.

1 MS. MULLER: Okay. So these are FAB fragments that this is
2 expressing, but they're actually being packaged together within the same
3 particle. So each phage particle has a heavy chain fragment and a light chain
4 fragment within it. So when it's actually extruded out of the bacterium into
5 the periplasmic space, what's happening is you're coming out with a particle
6 that already has a heavy chain and a light chain together in the same particle.

7 The other difference is in the prokaryotes in the bacteria phage
8 display example, the components are actually getting shuttled into the
9 periplasmic space of a bacterium. So your heavy and light chain component
10 are right there, even if they wouldn't be optimally matched. For example,
11 they could bond through their disulfide bonds if there was something in their
12 variable regions that perhaps made them not amenable to pairing. They're
13 still in an area where even if they didn't have the best binding abilities for
14 each other to pair with each other, all the components are still there, as
15 opposed to in the eukaryotic cytoplasm where you're expressing from two
16 separate vaccinia viruses.

17 JUDGE LEBOVITZ: Okay. So you're saying that because of
18 the Cre-lox system in the phage, and this may not be relevant, but they
19 actually got put together. Right?

20 MS. MULLER: They are packaged in the same bacteria phage.

21 JUDGE SCHEINER: So they almost can't miss each other is
22 what you're saying.

23 JUDGE LEBOVITZ: Right.

24 MS. MULLER: They're right next to each other. When that
25 phage protein gets expressed, the periplasmic space between the membranes

1 of a bacterium, all those proteins when they get expressed get shuttled into
2 that membrane and are right there.

3 JUDGE LEBOVITZ: They're in the same phage vector?

4 MS. MULLER: Yes, well, the DNA encoding those are in the
5 same phage vector.

6 JUDGE LEBOVITZ: Yes, right. Exactly. But I mean
7 analogously, though each cell -- and I don't want to get off point -- but each
8 cell actually would have one plasmid and another plasmid, and so they would
9 be next to each other or they would be, if you put them on strong promoters,
10 they're the only things getting expressed in that cell, just as those are the only
11 proteins getting expressed in that phage.

12 MS. MULLER: The difference I would say is that even if you
13 try to control for some things in the eukaryotic system, they're still not getting
14 put together the way the periplasmic space is assembling the prokaryotic
15 system.

16 JUDGE LEBOVITZ: Right. Okay. Right.

17 JUDGE ADAMS: So on the surface -- no pun intended here.
18 On the surface while the phage system looks like a corollary to the vaccinia
19 system, they're really, truly fundamentally different in the way they package
20 and process the material. Is that right?

21 MS. MULLER: Correct.

22 JUDGE ADAMS: And for that reason, a person of ordinary skill
23 in the art who would be familiar with vaccinia and who would be familiar
24 with phage know these differences wouldn't see them as being something that
25 you can easily or obviously just say, oh. Well, if you can do it in phage, you
26 can obviously do it in some eukaryotic viral system like vaccinia.

1 MS. MULLER: Absolutely. And that's what Dr. Storkus was
2 exemplifying was that at the time he was sitting at the scientific advisory
3 board when the invention was presented and was recalling at the time, well, I
4 don't think this is going to work in eukaryotic cells, but.

5 JUDGE ADAMS: And Rowlands doesn't help us because it's
6 just using one antibody. It's basically using vaccinia as an expression vector
7 for that one, to produce that one antibody. Is that right?

8 MS. MULLER: It's producing a single antibody, extensively
9 characterized, and just trying to make more of it.

10 JUDGE ADAMS: Which is something different than the phage
11 system where we're using libraries to produce the combination and a variety
12 of different antibodies. Is that right?

13 MS. MULLER: Correct.

14 JUDGE LEBOVITZ: And just to be clear in the Declaration for
15 example by Dr. Storkus, he gave his opinion that it would be unexpected or
16 unpredictable. And then he argued as you just did about the reason why it
17 would be unpredictable, because the phage -- then he gave some other reasons
18 for it. So it wasn't just an opinion. It was an opinion where he gave some
19 factual reasons for it.

20 MS. MULLER: It was based on his knowledge of how phage
21 display works, his knowledge of how the eukaryotic system works. And also
22 he submitted a reference by de Haard et al that also is a sub exhibit of his
23 Declaration, and that reference --

24 JUDGE LEBOVITZ: Which reference is that?

25 MS. MULLER: It's by Hans J. de Haard. It would have been a
26 sub exhibit after that industry survey after the end of Dr. Storkus's.

1 JUDGE SCHEINER: Okay. But was that mentioned in the
2 Declaration?

3 MS. MULLER: Yes, it was mentioned at paragraph 9 of the
4 Storkus Declaration on page 6, paragraph 9. He mentions that he submitted
5 this. He's aware that others have done working with phage display fragments.

6 JUDGE SCHEINER: Okay. I saw that. That's not the Kaloff
7 reference. Is it? That's all right. We'll find it.

8 MS. MULLER: Okay. What I wanted to --

9 JUDGE SCHEINER: There are certain references that are
10 mentioned specifically in the Declaration; and, I'm sorry. Go ahead.

11 MS. MULLER: Well, this de Haard reference from the "Journal
12 of Biological Chemistry" is talking about a different phage display system
13 that was developed.

14 JUDGE SCHEINER: Do you have a copy of the Declaration
15 that you're looking at? I want to be absolutely sure we're looking at the same
16 declaration.

17 MS. MULLER: Yeah.

18 JUDGE SCHEINER: Did Dr. Storkus?

19 JUDGE LEBOVITZ: I don't see that part.

20 JUDGE SCHEINER: Yeah. Did he submit more than one
21 declaration?

22 MS. MULLER: No, we just have one.

23 JUDGE SCHEINER: Would you mind if I?

24 MS. HOANES: May I approach?

25 JUDGE SCHEINER: Please. I just want to make sure we're
26 looking at the same thing, because I'm not convinced that we are. Thank you.

1 We are not. The one that's in our working file is a different Declaration.
2 That's the source of our confusion.

3 JUDGE ADAMS: When was that executed?

4 JUDGE SCHEINER: This one was executed --

5 JUDGE ADAMS: Well this was October 26 of '07, and then
6 there's that one.

7 JUDGE SCHEINER: 2007, and then this one was July 20, 2005.

8 We will get this. If this is the one that you're referring to in your Brief, we
9 will get it. There's been some kind of mix-up. The wrong Declaration is in
10 our working file. We will get the correct one.

11 JUDGE LEBOVITZ: But how do we know which one is
12 correct?

13 JUDGE SCHEINER: Well, it will refer to it in the Brief. Right?

14 We have a declaration, Dr. Storkus's Declaration, that was executed October
15 26, 2007. That's what we have in our working file, but we have access to the
16 entire file; and if it's clear from the Brief that you're referring to the earlier
17 one, we will certainly look at that one.

18 MS. MULLER: Okay.

19 JUDGE SCHEINER: Okay. Well, I'm glad that's -- but I can't
20 keep this, you understand. We have everything --

21 MS. MULLER: I understand.

22 JUDGE SCHEINER: -- in a larger electronic record.

23 MS. HOANES: That was actually copied from the electronic file
24 at the PTO.

25 JUDGE SCHEINER: Right, I know; but yeah, I understand. It's
26 just we have the evidence appendix. Let me just take a look at exactly what

1 the evidence appendix says that came with your Brief. Yes, okay. I
2 apologize. The wrong Declaration is in our working file and I didn't catch it
3 in the evidence appendix.

4 MS. HOANES: Okay.

5 JUDGE SCHEINER: So we will get the right one and give it full
6 consideration.

7 MS. MULLER: May I proceed with what I was going to say?

8 JUDGE SCHEINER: Yes, please, and I'm sorry. That's why I
9 was confused, because you were referring to a reference I hadn't seen. Okay.

10 MS. MULLER: Well, I'll give you the page number and just
11 give you this quote, and it will be available in the record.

12 JUDGE SCHEINER: Yes, okay. Well, don't be concerned. We
13 will give that Declaration full consideration.

14 MS. MULLER: The reference, it's on page 18218. Sorry, it's
15 JBC so it has a lot of pages. 18218, which is the first page of the reference
16 and it mentions here. "Key to the success of the technology, it's a reference
17 that is entitled "a large non-immunized human FAB fragment phage library
18 that permits rapid isolation and kinetic analysis of high affinity antibodies.
19 Key to the success of the technology were two critical observations: one, the
20 expression of functional antibody fragments by secretion into the periplasm of
21 escherichia coli, and it also confirms that the light chain" -- this is on page
22 18222.

23 JUDGE LEBOVITZ: Can you read slow?

24 MS. MURRAY: I'm sorry. Page 18222 is also talking about the
25 libraries and how they're expressed. And it says the light chain is expressed

1 as a separate fragment secreted into the periplasm where it can combine with
2 the heavy chain.

3 JUDGE SCHEINER: Okay.

4 MS. MURRAY: So it's showing that the periplasmic space and
5 the phage display is a key aspect of that technology. And Dr. Storkus's point
6 was that by --

7 JUDGE LEBOVITZ: Did Dr. Storkus comment in that
8 Declaration on the same issue of why you would not extrapolate it from the
9 bacteria phage to the vaccinia system?

10 MS. MURRAY: Yes. May I read it to you?

11 JUDGE LEBOVITZ: Hm-hmm.

12 MS. MURRAY: This is on page 3 of the Declaration. "I and the
13 other members of the SAB" -- Scientific Advisory Board -- "were aware of
14 reports that this could be done for libraries of antibody fragments expressed in
15 phage. This did not, however, convince us that good antibodies could be
16 selected in eukaryotic cells, because one, the throughput for screening phage
17 exceeded the expected throughput for screening libraries expressed in
18 eukaryotic cells by as much as four orders of magnitude. Two, most of the
19 work reported with antibody fragments expressed in phage was carried out
20 with single chain Fv (scFv) in which the variable regions of immunoglobulin
21 heavy and light chains are covalently linked, thereby increasing the likelihood
22 that they will associate. This is significant because one of the concerns raised
23 in the SAB was that antibodies are efficiently assembled and expressed in
24 mature B lymphocytes, or the natural human system, because their component
25 immunoglobulin heavy and light chains have been selected to pair properly.

1 In contrast, we thought that random pairs of immunoglobulin
2 heavy and light chains derived from separate libraries would be poorly
3 matched and would therefore fail to associate properly in the eukaryotic
4 cytoplasm. A related point is that antibody fragments expressed in phage,
5 whether or not the immunoglobulin heavy and light chains, variable regions,
6 are covalently linked, concentrate and are assembled in the periplasmic space.
7 The conditions of assembly in the eukaryotic cytoplasm are far different from
8 those that apply in the periplasmic space, and it could not be known what
9 effect this would have on antibody assembly."

10 JUDGE SCHEINER: I'm sorry to interrupt, but actually this part
11 was repeated in the Declaration that we have. This seems to be a
12 supplemental. Now that I look at it, it seems to be a supplemental declaration
13 to clear up the date as to when he considered this technology.

14 MS. MURRAY: Okay.

15 JUDGE SCHEINER: Yeah. Because apparently that wasn't
16 explicit in the first one, but the first Declaration also made reference to some
17 references that aren't in this one, so that's the source of the confusion.

18 MS. MURRAY: Okay.

19 JUDGE SCHEINER: Okay. So.

20 JUDGE ADAMS: Anything else?

21 JUDGE SCHEINER: I think we understand the issue.

22 MS. MURRAY: So any further questions?

23 JUDGE SCHEINER: Do you have anything further?

24 JUDGE ADAMS: No.

25

1 JUDGE SCHEINER: Thank you for coming in. I'm glad you came in,
2 because that was my fault for not noticing that it was not the correct
3 declaration, and I'm glad we cleared that up.

4 MS. MULLER: All right. Well, thank you very much for your
5 time today. I appreciate it.

6 JUDGE SCHEINER: Thank you for coming in.

7 Whereupon, at 2:50 p.m., the proceedings were concluded.

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